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THEORY OF THE ERADICATION OF MALARIA

G. MACDONALD, C.M.G., M.D., F.R.C.P., D.P.H., D.T.M.

Director, Ross Institute of Tropical Hygiene, London, England
Professor of Tropical Hygiene,
London School of Hygiene and Tropical Medicine

SYNOPSIS

The natural disappearance of malaria from certain areas—a phenomenon which has for many years been observed in various parts of the world—is discussed in relation to the recent deliberate elimination of the disease from large tracts of land. The process of elimination, the detection of residual foci, and the ways in which the disease may be reintroduced into a country are outlined briefly, and the course of events in epidemics which arise from small origins is described in detail. The factors affecting the basic reproduction rate in such epidemics—mean duration of infectivity of a primary malaria case, density of mosquitos in relation to man, and longevity and degree of anthropophilism of the vector concerned—are analysed, and a simplified method of expressing this rate mathematically is given in an annex.

General Observations

The concept that malaria could be totally eliminated from an area is an old one and has its background in a natural phenomenon, incorrectly known as the " spontaneous " regression of malaria, observed in very many parts of the world. This concept, for some years supported by a number of examples of deliberate elimination from small areas, has been reinforced recently by the successful eviction of the disease from large tracts of land —a result which shows that the natural happenings can be simulated by deliberate effort. The order of events under natural conditions is worth some study because it is likely to be repeated, though perhaps on quite a different time-scale, where the elimination is deliberate. Malaria reached a peak of endemicity in about 1750 in northern Europe and in about 1870 in North America, and thereafter declined. The decline, however, was not regular in either case, being marked by periodic exacerbations at about 20-year intervals and by irregular exacerbations at times when man's activities, particularly during wars in Europe, specially favoured the dissemination of the disease. Despite these recrudescences, however, regression proceeded, the disease disappearing from one large part of an area after another, but leaving foci in which it persisted for a long time. These foci have repeated in miniature the history of the countryside as a whole, the

malaria in them showing periodic cyclical rises but a general tendency to recession. Apart from these semi-permanent foci, evanescent outbreaks of the disease have occurred throughout the territories. Some of these outbreaks have been inexplicable; they have sometimes reached considerable proportions before diminishing and finally disappearing as inexplicably as they appeared. Others have had accountable causes. Such epidemics have rarely attracted much general interest, but the accounts of those which have apparently been spontaneous—for example, the outbreaks in the Netherlands recounted by Swellengrebel [18]—are of special interest in the context of artificial elimination.

The causes of these natural disappearances are very difficult to trace, and over-ready explanations should be discouraged by a study of the highly analytical paper by Brumpt [3] in which most of the commonly accepted reasons are discredited. They do, however, show that small changes in the environment can in some circumstances cause the disappearance of the disease from places which were previously considered excessively malarious. The fact that this possibility is not confined to temperate zones is shown by present events in Malaya, where the disease has been receding at a progressively increasing rate for ten or more years, quite independently of the deliberate action of man, and has regressed to a sufficient degree to have reduced malaria to a relatively minor disease in that country.

The process of elimination

The deliberate elimination of malaria was achieved in a number of small areas, for example, in Bermuda, 30 years ago. It has, however, recently been achieved over large land masses. The malaria-control programme of the USA was planned with the express intention of effecting large-scale eradication—an end which has since been reached. An earlier campaign, carried out in Crete, had less certain origins but an equally decisive end, while, more recently, the same result has been attained in a large part of Venezuela [9] and possibly in parts of the Guianas. The primary lessons of these successful campaigns are that enhancement of administrative control and of epidemiological understanding are more important than any specific modification in technique; that an original general attack must give way to a highly selective attack based on epidemiological studies; and that, in the countries mentioned at least, reintroduction or recrudescence has been very much rarer than was expected by many. The process is now to be extended from these countries to a large part of the world's surface, and while the lessons of the previous campaigns are to be learnt and followed, there can be no slavish acceptance of details of procedure, because even small differences in the epidemiology of the disease might well make a great difference to the ease or difficulty of elimination and to the nature of the surveillance and emergency services necessary whilst it is being attained.

The object of the present paper is first to review the subject as a whole and then to study particularly the influence of different epidemiological characteristics to see how they might modify the procedures or the results to be expected from them.

In any country where malaria is widespread an elimination programme must inevitably start with a general malaria-control programme, which will normally be based on the application of residual insecticides according to now well-acknowledged techniques. Such programmes must continue throughout the malaria seasons for a sufficient length of time for at least the vast majority of cases of malaria to have been cured, naturally or artificially, while transmission was stopped. In places where vivax malaria is prevalent this will usually involve programmes covering three or more years, because in many countries there are no ready and safe means of effecting the cure of all cases more rapidly. It is to be recognized that malariae infections may persist for very long periods,[17] though the risk of epidemics due to them is probably small. In countries where falciparum malaria is predominant it is conceivable that the period of control could be very materially reduced—perhaps down to a period of months or the duration of one malaria season—because it is possible to obtain a radical cure of this infection with forms of treatment which can be widely administered without medical supervision. Some preliminary research on this subject, notably by Farinaud & Choumara [8] and by Vincke,[19] has given very promising results, which fully justify the carrying-out of further exploratory trials.

Whatever the mechanism of this initial programme a stage is reached where it is assumed, on the results of case-finding surveys and examination of infant parasite-rates, that transmission has come to an end completely and that the number of infective carriers has been reduced, if not to zero, at least to a very low level. It must at the same time be assumed, first, that this apparent elimination is not universal and that there are some undiscovered foci in which transmission continues; secondly, that there are in the general population some remaining carriers from whom dissemination might occur; and, lastly, that immigrants either from the residual foci or from outside the country might at any time reintroduce the disease. The object of an eradication programme must be to discover and eliminate the residual foci of transmission, and to recognize remaining carriers, or incipient epidemics arising from them, before they have reached proportions which are locally serious or which lead to dispersion elsewhere. The surveillance and emergency-service mechanism should be based on an appreciation of the probable order of events and, particularly, on the expected timing of epidemics arising from a small origin of one or two cases in a part of the countryside otherwise free from the disease. An examination of the theory of eradication therefore necessitates a study of the timing and scale of such epidemics, which will be presented later in this article.

Detection of residual foci

The detection of foci of continuing transmission presents mainly administrative problems. Intensity of effort, both in control and in the subsequent checking of results, will inevitably have been concentrated in places known to be highly malarious. There are almost certain to have been some errors in the appreciation of such places, and these errors are likely to be repeated in checking procedures unless some quite different technique of approach is followed. The position is analogous to that in mosquito eradication by larvicidal techniques where it is necessary to check by adult catches, which may reveal the presence of foci of breeding that have been repeatedly overlooked in larvicidal work. Residual foci are likely to display themselves by their residents' moving away and appearing as malaria cases in areas which are otherwise free. Such cases would be detected by a systematic collection of blood films from hospital out-patients and in-patients throughout the countryside, followed by a thorough epidemiological investigation of all positive cases to trace the probable source of infection. By such means the epidemiologist can be led to the residual foci, which may prove to be hamlets that were overlooked or inadequately treated in the general programme or to be groups of people who did not come under the influence of the control programme. Untreated or inadequately treated hamlets may lie in inaccessible places or in places considered non-malarious, and in tropical countries their very existence may not previously have been suspected. Groups of people who are more or less permanently migrant are likely to escape treatment, and it is not always realized that in every country there are considerable numbers of people whose lives are not normally led within four walls which can be treated with residual insecticides. The nature of these groups will vary from country to country. Surveyors and prospectors may be found consistently infected in one country, contractors' labourers habitually camping beside their work in another, etc.; while in most countries there are groups who wish to conceal the nature of their movements from the authorities and who need special detection. After the original haphazard findings of inadequately treated hamlets or groups of people, a pattern is likely to emerge from which a plan to discover other similar groupings can be derived. This work is likely to be extremely interesting; the nature of the foci will probably differ very much from one country to another, but it will not be greatly influenced by different epidemiological characteristics being governed rather by sociological characteristics.

Reintroduction of malaria

The reintroduction of the disease or recrudescence from very small origins is influenced very considerably by different epidemiological characteristics. Such a revival could happen anywhere and there can be no assurance of freedom from it, though it is likely to be more common during the

early than during the late stages of a programme. In studying the problem one must assume that reintroduction has taken place and examine what are the likely consequences and how they can be recognized at an early stage. An undue reliance on past natural happenings could in this connexion be deceptive. There are many records of natural epidemics, but they have for the most part occurred in places where the circumstances were naturally unfavourable to the disease. Eradication is, however, being attempted in places which are naturally extremely favourable to transmission, and recrudescence is to be expected from small origins and ought to be detected before it has induced even a moderate endemicity in the population. Past analytical studies do not necessarily cover the subject. The author has made some original analyses of the nature of epidemics [14] in which he attempted to explain the mechanism of outbreaks. These analyses were not claimed to be numerically exact, but it was thought that they explained the general form of happenings and the order of events leading up to them. In trying, however, to synthesize the Ceylon epidemics of 1934 and 1935 it was found necessary to start building on a substantial original prevalence (an initial parasite rate of 7.9% was eventually chosen) since, otherwise, no epidemic of the type which actually occurred could be built up under the conditions obtaining in the country. Any attempt to build epidemics from much smaller origins led to a wholly unrealistic timing or demanded the attribution of mosquito characteristics which were known to be incorrect. It has therefore been necessary to make a fresh study of the whole subject of the genesis of epidemics. The mathematical technique developed in the earlier paper has been used as a background and has been found to give consistent and realistic results, but fluency in working with techniques of this type has revealed certain short cuts which do not deviate greatly from accuracy.

Epidemics from Small Origins

The causes of an epidemic lie in a source of infection, a suitable temperature for the development of the plasmodia in the mosquito, and an anopheline community which is adapted to transmission in its susceptibility, biting habit, longevity and numbers. If these factors are favourable an epidemic results which may be described in terms of time of development and degree of severity.

The original source of an epidemic will probably be a chronic case of the disease. In vivax malaria this will often be a late relapse, which may be more likely to occur at some special season of the year; in falciparum malaria it will usually be a case of long-standing infection. Whichever it is, the source is likely to be a person with some immunity who does not suffer greatly from the disease and does not draw attention to himself, and may therefore escape observation. The immunity which makes detection difficult

will also probably make the original case relatively poorly infective, and the low degree of gametocytaemia will result in the infection of only a small proportion of the anophelines feeding on the case, and in only low-grade infections in many of them, which, in turn, will result in their being poorly infective to man. The number of secondary cases arising directly from this source is therefore likely to be relatively low. However, such secondary cases, though not numerous, will be non-immune and will display the characteristics of a fresh infection—notably, the prevalence of large numbers of highly infective gametocytes in the blood for a considerable period of time. Hence the true growth of an epidemic through the population may be considered to arise from the secondary infections.

On the introduction of such infective cases to a community, events follow in a series of phases rather than in a continuous sequence, the timing of the phase depending on the incubation interval of the disease. This interval is the complete period from the occurrence of infective gametocytes in one case to the development of infective gametocytes in the secondary cases derived from it. It includes the period of extrinsic development of the parasite in the mosquito; the pre-patent period, or incubation period as it is normally known, in man; and any interval between the patency of asexual parasites and the development of fully infective gametocytes. The last-mentioned portion of the incubation interval may be negligible in vivax infections, but it is certainly considerable in falciparum infections. Jeffery & Eyles,[11] studying two American strains of *Plasmodium falciparum*, showed that gametocytes became obvious on the 10th to 15th day of parasite patency and that they remained uninfective to mosquitos for a further period of 2-4 days ; a falciparum case is therefore not infective to mosquitos until at least a fortnight after the first appearance of parasites. Typically, therefore, the incubation interval in falciparum malaria is 36 days or more—12 days for the extrinsic development, 10 days pre-patent period in man, and a further 14 for the development of infectivity. In vivax malaria the incubation interval is probably normally of the order of 20 days, 10 days for the extrinsic cycle and 10 for the pre-patent period in man.

During the first phase cases increase by arithmetic progression, the number of new cases each day being about the same—a characteristic which accounts for the curious step or hesitation seen at the beginning of many natural epidemics. In the second phase cases increase by geometric progression, the number of new cases increasing each day as a reflection of the increase in the reservoir of infectivity during the previous interval. In the third and subsequent phases the rate of progression continues to increase until the number of susceptible individuals in the population is materially reduced and the multiplication of cases starts to decrease. The different lengths of these phases, corresponding to the incubation intervals, in vivax and falciparum malaria determine a difference in the timing of epidemics of the two diseases.

The rate of growth in the stages of arithmetic and geometric progression is determined by the reproduction rate of the disease; the mathematical expression of this rate, which was developed by Macdonald,[13] is given in the Annex (see page 384). In non-mathematical terms it is the number of infections distributed in a community as the direct result of the presence in it of a single primary non-immune case. The value of the basic reproduction rate depends on a number of factors, which may be considered separately.

(*a*) *The mean duration of infectivity in a primary case.* It is estimated that a period amounting in total to 80 days (not necessarily consecutive), corresponding to a recovery rate of 1/80 or 0.0125, might perhaps be taken as representative. Recent direct measurement by Jeffery & Eyles [11] in the case of falciparum malaria has shown that this figure may be used with reasonable confidence. The corresponding figures derived from the two strains of parasite investigated by these workers would be 73 and 122 days, and during the epidemic phase a variation of this order makes little difference. It should be noted that the figure for the mean duration of infectivity includes both the infectivity of the individual and the susceptibility of the mosquito, since these factors cannot be separated in such a figure.

(*b*) *The density of mosquitos in relation to man.* Clearly no figure can be generally applicable, but in working it has been assumed that one of the functions of the surveillance and emergency service would be to prevent an excessive prevalence of potential vectors, and a maximum density of 10 per person has been allowed for.

(*c*) *The frequency with which the vector bites man.* This is a compound of its biting frequency and anthropophilic habit, and appears in the basic reproduction rate in the squared form, representative of the fact that a mosquito must bite twice to convey infection from one person to another. Its range among known vectors is very considerable, and its influence on the basic reproduction rate is so enormous that it is impossible to group together conditions where the man-biting frequency is high and those where it is low. The characteristics of malaria in the two places would inevitably be greatly different, and this would not be shown anywhere more clearly than in the rate of development of epidemics.

(*d*) *The longevity of the mosquito.* The influence of this characteristic is as great as that of the man-biting habit, as is shown by the spectacular success of imagicidal measures. In the majority of the malaria vectors, however, the value probably lies within a narrower range than does the man-biting habit, the degree of natural variation being less. There are some exceptions to this : the longevity of *Anopheles pharoensis* probably lies well below the normal range, as does that of *A. aquasalis*. Moreover, even the small range within which the longevity lies in most species represents a considerable influence on transmission. There has unfortunately been very little effort made to measure this important characteristic, though

valuable information could have been extracted from quite simple observations when malaria was more prevalent. The ratio of the sporozoite rate to the total infection rate, sporozoites and oocysts, is probably a fairly accurate guide. All pre-existing data on this ratio are valuable, though they cannot of course be repeated during the present era of general control, the techniques now available demanding a more specialized entomological approach. Without such data it is to be assumed that the mortality of most vectors lies between 5% and 10% per day, i.e., that the probability of survival lies between 0.95 and 0.9. Longevity is an important factor in that it determines the probability of survival for a sufficient time for the sporozoites to develop and the subsequent expectation of life in which to convey the infection; the degree of this influence has been expressed numerically in a table previously published by Macdonald.[13, a]

If any idea can be gained of these values a rough picture of the basic reproduction rate can be built up. For example, if a non-immune untreated case is typically infective for 80 days and is exposed each day, on an average, to 10 mosquitos of which half bite man and which have a daily mortality of 10%, so that 30% survive for 12 days and have a subsequent expectation of life of 9 days, on half of which they will bite man, it can quite simply be worked out that such a primary case might infect as many as 540 secondary ones, and this would be the value of the basic reproduction rate. For the present purposes there is no point in making a precise estimate of this rate, only the general order of which needs to be understood, because in nature it may vary between one or two and some very large figure such as 5000.

The length of the incubation interval and the nature of the basic reproduction rate determine the scale of multiplication of positive cases in each interval. The mathematical connexion is complicated. A large number of synthetic epidemics have been worked out, using the full mathematical technique elaborated in a previous paper.[14] In the course of this work it was noted that, until the incidence becomes high, progression is very regular and nearly, though not exactly, of a simple multiplicative type. For the sake of simplicity, an empirical statement of the approximate nature of happenings is given here, and a justification of it is presented in the Annex.

First, let us consider the happenings in the case of an incubation interval of 20 days, which is taken as generally applicable for vivax malaria. Infective cases occur at zero time. For the period of one incubation interval there are no secondary cases. In the second interval the latter will occur, and in such numbers that at the end of it the proportion of the population affected will be represented by :

$$x_2 = x_1 (0.22z + 0.8)$$

[a] This table has been reproduced in the Annex to the article on page 613.

where x_2 is the proportion affected at the end of the period, x_1 is the proportion affected originally (the primary cases), and z is the reproduction rate.

In successive intervals after this, the proportion affected will be multiplied in a similar manner, except that the value of the factor by which z, the reproduction rate, is to be multiplied varies with the value of that rate in roughly the following way :

Reproduction rate	*Multiplication factor*
1- 3	0.20
4- 7	0.18
8-17	0.16
18-49	0.14
50 and over	0.12

Thus if the reproduction rate were 50, and the original cases amounted to one per thousand of population, or 0.001, the parasite rate would rise in one interval to 0.001×11.8, or 0.0118. In the subsequent interval this would be multiplied by 6.8 to 0.08, and again in the next to about 0.55, or 55%. The epidemic would then be at its peak some 80 days after the occurrence of primary cases and 60 days after the appearance of secondary cases derived from them. For a reproduction rate of 20, the course of events would be roughly as follows : at the end of the first interval, 0.001, and at the end of the second, 0.0052; thereafter, the value for the parasite rate at the end of the preceding interval is multiplied by 3.6 (2.8+0.8), thus giving rates of 0.019, 0.067, 0.243 and 0.873 at the end of the third, fourth, fifth and sixth intervals, respectively. In this case the apex of the epidemic would be reached near the end of the sixth interval, 112 days from the occurrence of the primary cases and 92 days after the first appearance of secondary cases. In this series the successive generations of secondary cases represent 0.4%, 1.4%, 4.9%, 17.5% and 63.1% of new cases in the population. It is clear that the last would constitute a locally calamitous epidemic of great severity, despite the fact that it arose from a relatively low reproduction rate. It follows, therefore, that a low reproduction rate will be revealed by the prolonged period of genesis of an epidemic rather than by any lack of severity in the epidemic itself. It would clearly be the function of a surveillance service to detect an outbreak of the type depicted above during the period of genesis, and certainly within the first two generations of secondary cases.

Comparable synthetic figures can be computed for any value of the reproduction rate, but to save laborious tables of figures a number have been constructed as epidemic curves in Fig. 1. These represent the total cases or parasite rate; the proportion of new cases in any interval is calculable by comparison of the proportions positive at the beginning and at the end. The timing of epidemics dependent on different reproduction rates can be readily judged from it. It may be noted that the second interval, the first in which secondary cases appear, is a time of at least relatively slow growth,

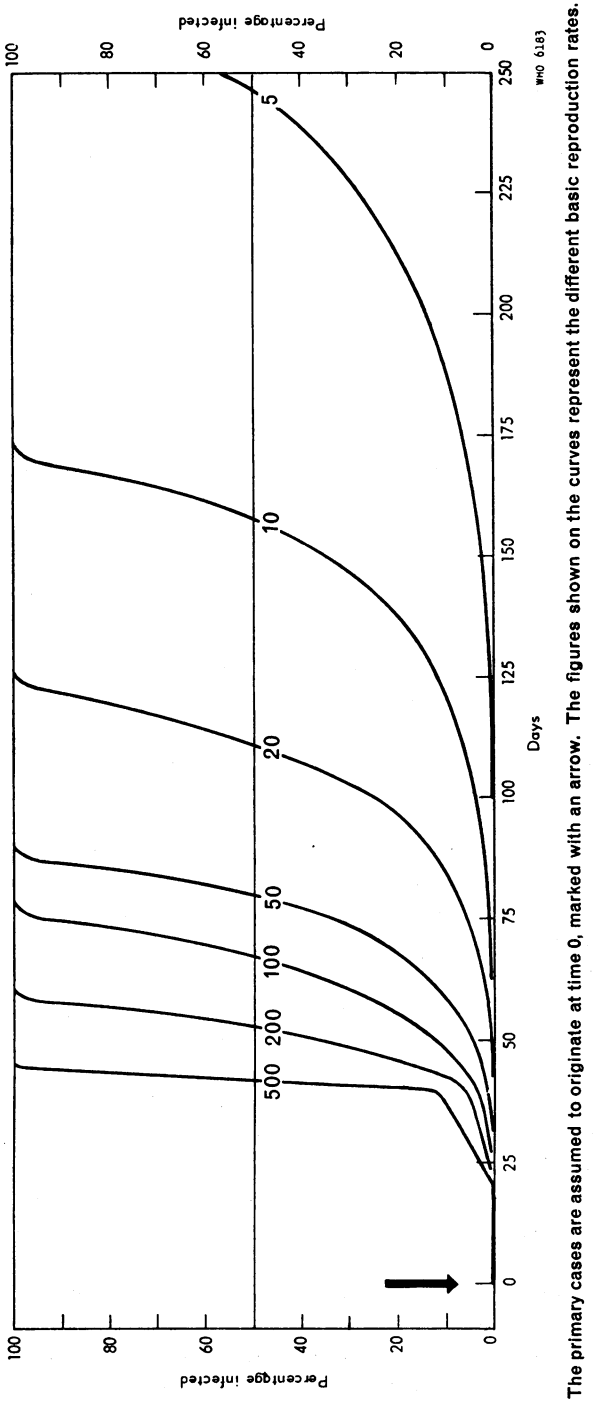


FIG. 1. PROBABLE GROWTH OF INFECTION RATE IN VIVAX EPIDEMICS (INCUBATION INTERVAL, 20 DAYS) FROM SMALL ORIGINS (0.1% OF THE POPULATION), SHOWING INFLUENCE OF BASIC REPRODUCTION RATE

The primary cases are assumed to originate at time 0, marked with an arrow. The figures shown on the curves represent the different basic reproduction rates.

whatever the causative reproduction rate; the dramatically steep rise does not come till later. When it does come, the people would notice little difference between one due to a low rate and one due to a high rate, the distinction being discernible only in the speed of events.

In outbreaks of falciparum malaria, events will follow a similar pattern, the detail, however, being altered by the much longer incubation interval, for which an average value of 35 days has been taken. Fig. 2 illustrates the probable happenings. The first cases would appear about 35 days after the appearance of a primary case or cases, thus initiating the second interval, at the end of which—35 days later—the proportion of the population affected might be represented by:

$$x_2 = x_1 \ (0.35z + 0.7)$$

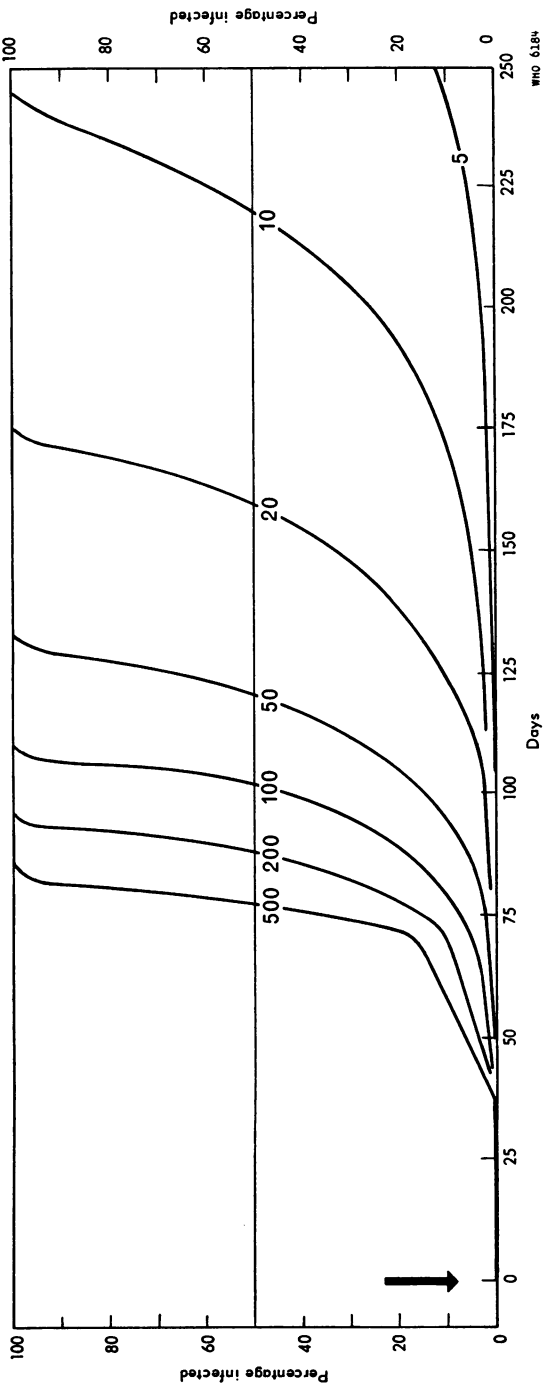
In each succeeding interval of 35 days the proportion would be multiplied in a corresponding way except that, as before, other figures have to be inserted in place of 0.35 in the above expression, as follows:

Reproduction rate	*Multiplication factor*
1- 3	0.30
4- 6	0.28
7- 9	0.26
10-25	0.24
26-49	0.21
50 and over	0.20

An epidemic in this series dependent on a reproduction rate of 20 may be explored as a parallel to that in the previous series. No secondary cases would occur for 35 days, so that the parasite rate would still be 0.001 at the beginning of the second interval. At the end of the second phase, 70 days from the origin, the parasite rate would be 0.0077, and at the end of the next two 35-day intervals it would be 0.042 and 0.233, respectively. The peak of the curve would come about a couple of weeks after this, perhaps 160 days after the introduction of primary cases, some 6-7 weeks later than in the previous case.

A comparison of Fig. 1 and Fig. 2 will show the consistent difference in timing to be expected in outbreaks of vivax and falciparum malaria; this is only a reflection of what has always been known to happen, though explanations have varied. Falciparum malaria is relatively slow in propagating and the peak of falciparum epidemics, which occurs when roughly half of the population is infected, will therefore appear later than that of vivax epidemics, even when transmission is intense. There is in both cases a phase of relatively slow growth, representative of the initial broken step often seen in epidemic curves, but if the proportion of the population affected at the end of it is moderate there is a sudden transition to a dramatic rise. When the origins are small, as is postulated here, the sudden rise occurs at this stage only if the reproduction rate is high; but if the origins

FIG. 2. PROBABLE GROWTH OF INFECTION RATE IN FALCIPARUM EPIDEMICS (INCUBATION INTERVAL, 35 DAYS) FROM SMALL ORIGINS (0.1% OF THE POPULATION), SHOWING INFLUENCE OF BASIC REPRODUCTION RATE



The primary cases are assumed to originate at time 0, marked with an arrow. The figures shown on the curves represent the different basic reproduction rates.

are larger, it can also occur then in epidemics where the reproduction rate is comparatively low. The initial relatively slow stage is a warning of what is to come in an exaggerated form, and towards its end it gives an indication of what is already incubating in man and mosquito. If secondary cases are recognized, a study should clearly be undertaken immediately to find out their numbers and the period for which they have been prevalent; the results of such a study will dictate the urgency with which emergency insecticidal and, perhaps, mass therapeutic measures should be introduced. Immediate therapeutic measures may be indicated if it is feared that any notable proportion of the people is incubating falciparum malaria, but if only vivax malaria is suspected it may be preferable to permit the development of actual cases at the time, when special treatment facilities can be provided, rather than to prolong the incubation period for months by abortive treatment and cause an outbreak of relapses later, when the sense of urgency has passed.

In many countries transmission is seasonal, the epidemic curves being cut short after a varying period, often about 150 days in the malarious Mediterranean zone; the importance of recrudescence would in such cases turn largely on the severity of transmission and on the time of its commencement. The past history of much of the Mediterranean lands suggests that normally there has been ample time for the full development of vivax epidemics within the transmission season. These epidemics, however, have usually arisen from greater origins than those postulated here, and outbreaks from really small origins might well be cut off before reaching their summit. Past records of the summer parasite rate among young children and of the relative prevalence of vivax and falciparum malaria will throw some light on this question, but it is to be remembered that past happenings have largely been tempered by communal immunity, which restricts the growth of the reservoir of infection and, hence, the speed of development of epidemics.

Reproduction rates in nature

There has been very little direct study of the value of the reproduction rate in nature. There can, however, be little doubt that this is the core of all epidemiology and that analysis of the approximate orders which are prevalent should be the first function of any entomological unit connected with either malaria control or a malaria elimination scheme. Such an analysis demands examination of both the man-biting habit and the longevity of the vector anopheline. The measurement of longevity is a very recent innovation and there is room for considerable development of techniques. It has, however, been shown that ways can be found of making reasonable estimates under natural conditions (Davidson [6, 7]). The technique of ampulla measurement developed by Davidson should be generally

applicable, but there is no reason to think that this approach would exhaust all the possible means of making estimates of longevity.

Though not the sole factor, undoubtedly the one which most commonly influences the value of the rate is the man-biting habit of the mosquito, on which data can be readily collected by accepted techniques in any country. The length of the gonotrophic cycle and the usual interval between feeds can be determined by entomological means, and the frequency with which man is chosen as a source of blood can be estimated by means of the precipitin test, which can be carried out with sufficient accuracy for this purpose in any reasonably equipped laboratory. To illustrate its importance a standard set of conditions may be postulated, a reproduction rate deduced from them and the influence of changes in the man-biting habit on that reproduction rate examined. Under the standard conditions the probability of a mosquito's surviving through one day might be 0.9, the mosquito density in relation to man 10, the length of the extrinsic cycle of vivax malaria 9 days, and the normal duration of infectivity in man about 80 days, giving a recovery rate of 0.0125. If the vector anopheline bit once in every two days, and invariably chose man, the man-biting frequency would be 0.5 and the basic reproduction rate would be of the order of 735. In a place where these conditions ruled, malaria transmission would be severe, and if the transmission season were long malaria would be of the hyperendemic or holoendemic type. Any epidemics which arose during a process of eradication when the population was non-immune would be rather more severe than the sharpest shown in Fig. 1. If, however, the anthropophilic index were not 100% but 50%, the rate would be 184, and if it were 25%, 10% or 5% the corresponding rate would be 46, 7 or 2; the rate of growth of an epidemic dependent on these last figures would be extremely slow.

Variation in the mosquito density would produce very much less dramatic differences. A density reduced to one-tenth of that taken as the standard above would give a reproduction rate of 73, and a density of 0.1 would give a value of 7.

Variation in the probability of survival has a marked effect, but the usual range in nature is probably fairly narrow. Reduction of the figure of 0.9 used in the standard example, to 0.8, 0.7 and 0.6 would reduce the rates from 735 to 120, 23 and 4, respectively. This type of reduction is readily secured by insecticidal techniques, but the majority of natural vectors have a probability of survival exceeding 0.8. The influence within the natural range is, however, of sufficient importance to justify the special entomological study which has been recommended.

The distribution of past epidemics in relation to anopheline characteristics has been studied previously.[14] It has been shown that epidemics are closely related to instability of the disease, which is in turn dependent on either a low anthropophilic index or a low probability of survival. These

factors are also associated with low reproduction rates, and it has therefore happened that most natural epidemics have occurred in places where the reproduction rate has tended to be low. A number of outbreaks which the author studied previously have been reviewed in this light. The apparent severity of an epidemic is a poor guide, for whatever the cause of an epidemic, it may ultimately rise to an outbreak affecting simultaneously a large part of the population and be looked upon as dramatic. Distinction between epidemics lies in the rate of growth, which is most revealing when studied before the peak is reached, at which time the progressively increasing overlap of infections in man and the mosquito have already slowed it down considerably. Re-examination of the Ceylon epidemic previously analysed suggests that it may have been due to a reproduction rate of about 10. Actually, a value of 7.9 was chosen in synthesizing a comparable curve, but it is true that a better match might have resulted from a slightly higher figure.

The Delhi epidemic described by Covell & Jaswant Singh [5] appears to have been due to a reproduction rate of about 10; the Sindh epidemic, on which Covell & Bailey [4] collected extensive data, to one of about 4 or possibly less; and the African high-altitude epidemics described by Garnham [10] to one of about 10 or less. The Maracaibo epidemic described by Nieto Caicedo [15] may well have been due to a rate as high as 40. The singularly well-documented account of the reintroduction of malaria into Gran Canaria (Sastre [16]) shows that the epidemic was probably at first subject to the very high rate of nearly 100, for two primary cases produced 65 secondaries in a month. This outbreak occurred among a group of railway workers noted as living in rude temporary shelters, just the circumstances in which a normally zoophilic mosquito might be compulsorily deviated to man and cause a high rate. The disease was subsequently disseminated around the island, but clearly under the influence of a much lower rate, below 10.

The great majority of naturally occurring epidemics probably follow this pattern; they are attributable to relatively low reproduction rates, and if they arose from small origins should be sufficiently slow in early development to make recognition by an efficient surveillance system simple. It is to be remembered, however, that epidemics have in the past prevailed almost exclusively in places where there is some natural obstacle to transmission, whereas malaria eradication is to be practised both in these areas and in those where no obstacle to transmission exists and high reproduction rates are to be expected. Such free transmission is normally due to marked anthropophilism, combined with considerable longevity, in the vector. In places where these values are high, insecticidal control should not be abandoned until there is reasonable certainty of elimination, and a surveillance service should be established which could without any doubt detect recrudescence within, at most, a couple of weeks of the occurrence of secondary cases.

Annex

BASIS FOR MATHEMATICAL EXPRESSION OF REPRODUCTION RATE IN EPIDEMICS FROM SMALL ORIGINS

Statements of the sequence of probable happenings in the course of a malaria epidemic have been presented by Armitage [1] and by Macdonald.[14] Epidemic data and their mathematical analysis have since been examined by Bailey,[2] who favours the stochastic approach rather than the deterministic approach here adopted. The distinction lies partly in the degree of freedom of infectivity, i.e., whether the latter is restricted to a limited number of residents in a house or similar "cell" or whether it covers the community as a whole. It is thought that the deterministic approach is reasonably applicable to a disease carried by insects which move from house to house, and that the original approach may be considered valid.

The full technique of analysis previously described [14] has been used to work out a large number of synthetic epidemics. No simplification of an admittedly complex matter is possible if the full range of happenings is to be considered. Present interest lies, however, largely in the initial happenings in epidemics arising from small origins, at times when x is small. During this period a simplification can be adopted with little loss of accuracy, by ignoring the effect of overlap of infections in the mosquito which is at that time very occasional.

The following symbols are used:

- x = the proportion of the population affected; the subscripts 0, 1, etc. indicate the proportion affected at serial intervals of time representing the ends of successive incubation intervals.
- y = the proportion of total time lived, within one incubation interval, in an infective state.
- r = the recovery rate (numerically taken as 0.0125).
- i = the incubation interval, as defined in the text (see page 374).
- m = the anopheline density in relation to man.
- a = the average number of times a mosquito bites man in one day.
- b = the proportion of anopheline mosquitos with sporozoites in their salivary glands which is actually infective.
- p = the probability of an anopheline's surviving through one day.
- n = the time taken for completion of the extrinsic cycle.
- h = the proportion of the population receiving infective inocula in one day.
- z = the limit of the reproduction rate when x is infinitely small, or

$$\frac{ma^2bp^n}{-r\log_e p}$$

It is assumed that the epidemic arises from the appearance of one or more primary cases representing x_0—a small proportion, taken in the examples given as 0.001—and that these remain infective for the period of one incubation interval. x_1 then equals x_0, the incubation interval having delayed the appearance of secondary cases. The inoculation rate is then represented by

$$h = \frac{ma^2bp^n x_0}{ax_0 - \log_e p} \qquad \ldots\ldots 1$$

but while x_0 is low the value ax_0 in the denominator can be ignored with impunity, and

$$h \simeq \frac{ma^2bp^n x_1}{-\log p} \quad \ldots\ldots 2$$

$$\simeq rzx_1 \quad \ldots\ldots 3$$

$$\text{while } h/r \simeq zx_1 \quad \ldots\ldots 4$$

$$x_2 \simeq zx_1 (1 - e^{-ri}) + x_0 e^{-ri} \quad \ldots\ldots 5$$

$$\simeq x_1 [z(1 - e^{-ri}) + e^{-ri}] \quad \ldots\ldots 6$$

which is the basis for the statement of the ratio x_2/x_1, where for vivax malaria ri is taken as 0.25 and for falciparum malaria it is taken as 0.4375.

Continuing the same simplification,

$$y_2 \simeq x_1 \left[\frac{z - (z-1)(1 - e^{-ri})}{ri}\right] \quad \ldots\ldots 7$$

and from equations 6 and 7 a ratio, y_2/x_2, can be calculated and symbolized as d_2. Then

$$x_3 = x_2 [d_2 z(1 - e^{-ri}) + e^{-ri}] \quad \ldots\ldots 8$$

and

$$y_3 \simeq x_2 \left[d_2 z - \frac{(d_2 z - 1)(1 - e^{-ri})}{ri}\right] \quad \ldots\ldots 9$$

from which, again, a similar ratio, y_3/x_3, can be calculated and designated d_3. This process can be repeated in successive incubation intervals. Empirical working of actual values shows that the numerical values of d_1, d_2, d_3, etc. are dependent on z, and converge from an origin of 1.0 on a finite limit slightly exceeding 0.5. Corresponding values of d_3, d_4, d_5, etc. are found to be very close to each other though not identical.

These series have been graphed, and from the graphs the values of d to be inserted in putting forward the relation between successive values of x_2, x_3, x_4, etc. have been obtained. Comparison of curves drawn by this simplified technique and by the full technique has shown that the difference is immaterial while x is low.

RÉSUMÉ

L'endémie paludéenne a atteint son paroxysme au milieu du XVIII^e siècle en Europe septentrionale et vers 1870 en Amérique du Nord. Elle a diminué graduellement depuis lors, non sans de brusques recrudescences tous les vingt ans environ et quelques flambées favorisées par les mouvements de population et les guerres. En reculant, la maladie a laissé derrière elle de petits foyers, qui ont été à l'origine de poussées épidémiques. Les causes du recul naturel de l'endémie sont mal connues et les hypothèses avancées pour l'expliquer peu satisfaisantes. Cette régression spontanée n'est pas le fait des seules régions tempérées. Elle se produit actuellement, à un rythme accéléré depuis une dizaine d'années, en Malaisie, où, indépendamment de toute intervention humaine, la maladie a cessé d'être un problème majeur de santé publique.

La lutte contre le paludisme en vue de sa suppression a été entreprise, dans des régions limitées, il y a trente ans déjà, et réalisée avec succès depuis lors en Europe et dans les Amériques. Les expériences faites au cours des premières campagnes, qui ont mis en

évidence la nécessité de connaissances épidémiologiques précises et d'un contrôle bien organisé, ont inspiré les programmes plus récents d'éradication dans d'immenses régions du monde.

Actuellement, tout programme d'éradication du paludisme endémique débute par l'application d'insecticides à effet rémanent, renouvelée aussi longtemps qu'il est nécessaire pour supprimer la transmission et permettre la guérison des cas. La durée de la période de lutte varie selon le type de plasmodium responsable de l'épidémie. A la suite de ces campagnes intensives, il arrive un moment où la transmission cesse et où le nombre des porteurs de parasites devient insignifiant, ainsi que l'indiquent les enquêtes cliniques et l'indice parasitaire des enfants. On admet toutefois qu'il reste quelques foyers ignorés où la transmission se poursuit, où vivent quelques sujets infectants, qui pourraient réintroduire l'infection dans la zone indemne. Un programme d'éradication doit rechercher ces foyers, et déceler à leur début les épidémies auxquelles ils peuvent donner naissance. Il faut alors tenir compte des habitudes et du genre de vie des populations, ainsi que des conditions sociologiques, afin d'intervenir aux époques propices et dans les endroits — souvent perdus — où des foyers peuvent se créer ou avoir subsisté.

A l'origine d'une épidémie se trouvent réunies certaines conditions: une source d'infection, une température favorable au développement du parasite chez le moustique et une population d'anophèles bons vecteurs. La source de l'épidémie sera souvent un cas chronique, partiellement immun, asymptomatique et insoupçonné. Le nombre de cas secondaires dérivés de ce cas initial sera faible, mais comme il s'agit de sujets non immuns, ces cas pourront être la cause réelle du développement de l'épidémie. On peut distinguer dans la progression de l'épidémie trois phases, de longueur différente suivant le parasite en cause. Durant la première et la deuxième phase, où le nombre des cas augmente en progression arithmétique et géométrique, respectivement, l'épidémie s'étendra en fonction du « taux de reproduction » de la maladie, c'est-à-dire du nombre de cas dans une collectivité dérivés directement d'un cas primaire non immun. Ce taux, qui peut être calculé par une formule mathématique, dépend de plusieurs facteurs, en particulier de la durée de la période d'infectivité du cas primaire, de la densité anophélienne par rapport à la densité humaine, de la fréquence de la piqûre et de la longévité du vecteur.

L'étude du «taux de reproduction» dans les conditions naturelles a été peu poussée encore. Elle est pourtant au centre des phénomènes épidémiologiques responsables de l'épidémie. L'auteur analyse, de ce point de vue, certaines des épidémies des vingt dernières années. Le taux était de l'ordre de 10, parfois de 4. Cet ordre de grandeur paraît valable pour la plupart des épidémies spontanées qui se sont produites dans des régions où existaient des obstacles naturels à la transmission. Le taux est beaucoup plus élevé lorsque la transmission ne rencontre pas d'obstacle, du fait qu'elle est assurée par une espèce de moustique de grande longévité et fortement anthropophile. Dans ces conditions, la lutte au moyen des insecticides doit être poursuivie jusqu'à l'élimination à peu près certaine de l'infection et un service de surveillance doit être établi qui permette de déceler les cas secondaires dès leur apparition.

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